Restricted

NAVY DEPARTMENT

BUMED NEWS LETTER

a digest of timely information

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TABLE OF CONTENTS

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Penicillin Treatment in Late Syphilis: A study (Stokes et al.) of penicillin in the treatment of late syphilis, including neurosyphilis, congenital syphilis, late benign and visceral syphilis, and syphilis in the pregnant woman, has now reached an aggregate of 90 cases, of which approximately 50 per cent are cases of neurosyphilis.

Four of the total of 11 pregnant women with early syphilis have been delivered, and serologic and clinical follow-up thus far indicates that all the children are healthy. Nine mothers are showing a satisfactory decline of serologic titer towards normal, which should be indicative of cure. The

symptomatic results in general paresis have been closely studied by Dr. Gammon, and the remarkable effectiveness of penicillin in inducing remission in patients with the less deteriorated types of the disease is clearly demonstrated. Certain highly resistant manifestations such as persistent and severe lightning pain have shown striking response in three out of four cases.

Benign late syphilis of the skin and bones is so easily responsive to treatment that one-third the Mahoney initial dosage (1,200,000) for cure in early syphilis suffices to bring about complete healing. The curative effects in neurosyphilis are plainly demonstrated by serial spinal fluid examinations in which even Grade III fluids have been reduced to normal by 1,200,000 units.

Interstitial keratitis - a very complex problem, shows a variable response, strikingly favorable in some cases, indifferent or even slightly unfavorable in others. No case of optic atrophy has been made worse, and at least one has shown some evidence of improvement with marked response in the spinal fluid. A number of questions remain to be studied, including the relative effectiveness of large initial and moderate initial dosage, the effect of re-treatment, the avoidance of Herxheimer reaction, especially in the nervous system, and the permanency of the cure of syphilis in pregnant women. (OEMcmr-275.)

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Protein Intake in Hot Climates: "It is commonly thought that the protein intake should be limited in hot climates because of the stress the specific dynamic action of protein places on the heat-dissipating mechanism. It is easy to show that the ingestion of a large protein meal increases the load on the heat-dissipating mechanism during a march at the standard Army rate by not more than 5 per cent. Theoretically, in a critical situation this slight increase might have some effect, but actually a high protein diet produces no demonstrable effect on the ability of men to carry out work in the heat. This question has been carefully studied at the Fatigue Laboratory (University of Minnesota). No difference in the work performance in tropical conditions could be detected in subjects who were eating 60 grams of protein a day as compared with subjects eating 150 grams of protein a day." (Taylor, Bull. Minnesota M. Foundation, May '44.)

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Thiouracil in the Treatment of Hyperthyroidism: Experimental work designed to determine the value of thiouracil in preoperative and nonoperative treatment of hyperthyroidism is being carried on in a number of civilian clinics.

Most workers with the drug agree (Astwood, Means, Williams and Clute and others) that thiouracil is superior to iodine in the preparation of the hyperthyroid patient for operation. Thiouracil, as compared with iodine, acts more slowly, but in almost every case - regardless of the type of thyrotoxicity or of previous treatment - eventually reduces the basal metabolic rate to normal. In the average case from 3 to 5 weeks are required to achieve maximum response. During the period of preoperative administration of the drug, the patient may remain ambulatory but must have adequate rest and a high caloric diet supplemented by vitamins, especially those of the "B group." The return of the basal metabolic rate to normal is accompanied by a reduction in the plasma protein-bound iodine and a corresponding disappearance of clinical symptoms of the disease.

Since thiouracil decreases the quantity of thyroxin in the thyroid gland, in cases treated with this drug there is potentially less thyroxin to get into the blood stream at the time of operation than in cases treated with iodine and potassium iodide. Iodine used before or during thiouracil administration has not been found to be of value. Patients who have recently been given iodine seem to respond a little more slowly to thiouracil than do those who have not. The slight exacerbation of the disease which sometimes appears when thiouracil is suddenly substituted for iodine may be accounted for by the fact that iodine causes storage of the hormone in the thyroid gland and that significant amounts of the hormone may escape into the blood stream. Therefore, when changing from iodine to thiouracil therapy, the iodine should be continued in gradually diminishing doses for a period of about two weeks.

The effective dose of thiouracil varies in different patients. A good initial dose is 0.2 Gm. three times daily for the first two weeks, followed by 0.2 Gm. twice daily until the metabolism is normal and then 0.1 Gm. twice daily. In patients subjected to prolonged administration of the drug, it is sometimes possible to reduce the dose to 0.1 Gm. daily.

Thyroid glands removed at operation following preoperative preparation with thiouracil are firmer than normal, have a rubbery consistency and are more friable. There is a scarcity of colloid, the tissue consisting of an almost solid sheet of cells in many areas. Many acini appear small and contracted, while a few have enlarged lumens and these are apt to show papillary projections. The cells are tall and columnar. There is an increase in interstitial tissue, with a noticeable increase in fibroblasts, lymphocytes and collagen. In many cases the changes described, though present, are not marked. Previous use of iodine may modify the changes. The thyroxin iodine is found to be extremely low in most of the glands analyzed.

Means recently stated that although thiouracil will probably largely replace iodine in the preparation of patients for thyroidectomy, he doubted that it would replace thyroidectomy in the treatment of hyperthyroidism.

A fairly large number of patients have been maintained on thiouracil over long periods of time without operation. In most, the response has been satisfactory. Some have had relapses when taken off the drug, others have not. In some the use of thiouracil has had to be discontinued because of the development of untoward effects. These include agranulocytosis, urticaria, fever and other symptoms of hypersensitivity. Patients receiving the drug should be carefully watched, and the blood count should be frequently checked.

Thiouracil causes a decrease in the protein-bound iodine of the blood and in the thyroxin iodine of the thyroid gland, but does not inhibit the hypermetabolic effects of preformed thyroxin. These facts indicate that thiouracil inhibits the production of the thyroid hormone, but the exact process by which this is accomplished has not yet been determined. Presumably, when the production of the thyroid hormone is markedly inhibited, there results an excessive production of pituitary thyrotropic hormone, which in turn causes hyperplasia of the acinar cells of the thyroid and may cause certain manifestations of malignant exophthalmos. Thus, as has been observed in several cases, with the use of thiouracil in excessive quantities in thyrotoxic patients a still greater enlargement of the thyroid gland may result and the manifestations of malignant exophthalmos may be accentuated. Under such circumstances it is advisable to reduce the dosage of thiouracil. In some cases, however, the simultaneous administration of desiccated thyroid seems indicated, since it inhibits the production of thyrotropic hormone.

By accurately regulating the dosage of thiouracil it is believed that the goitrogenic effect can be kept low. In fact, in most cases the gland tends to decrease in size. In spite of the fact that many thyroid glands have decreased in size with treatment, it is not considered advisable to give prolonged thiouracil treatment to a patient who has an extremely large gland since there is some possibility that the gland will actually become larger. Since some of these patients have compression of the surrounding structures, the risk of further trouble should not be forgotten. However, the drug has been used preoperatively in some patients with extremely large glands. In fact the gland of one patient weighed 500 Gm. at operation in spite of a decrease in the neck circumference of 2.5 cm. during treatment. In this case, as in somewhat similar ones, desiccated thyroid was used with the thiouracil.

It is apparent that much more will have to be learned before the place of thiouracil in the medical treatment of thyrotoxicosis can be fully evaluated.

(In the preparation of the above item the paper of Williams and Clute, New England J. Med., June 1, '44, has been freely used and in part quoted.)

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Thiouracil is not commercially available. Limited amounts for clinical trial may be obtained from the Lederle Laboratories, Pearl River, New York.

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Metatarsalgia: Baker and Kuhn report curing 14 cases of Morton's metatarsalgia by removing tumors of the fourth plantar digital nerve lying in the web space between the third and fourth toes. This syndrome is characterized by pain localized in the fourth metatarso-phalangeal articulation. The etiology of this lesion is questionable, but the anatomical relationships of the nerve and the pathological findings indicate that it is a degenerative fibrosis of the nerve with neuromatous proliferation resulting from, or irritated by, repeated trauma. The characteristic history of the syndrome and the presence of a localized tenderness on deep palpation in the third web space or between the third and fourth metatarsal heads on the dorsal surface of the foot make the diagnosis simple. Excision of the tumor relieves the symptoms. (Southern M. J., March '44.)

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Protection by Methionine against Hepatic Injury: The fact is now well established that the protein-depleted liver is more vulnerable to hepatotoxic substances than is the normal liver.

Miller and Whipple (1) showed that liver injury due to chloroform anesthesia increases in extent as the body stores of protein are depleted. They demonstrated also that a single large protein feeding protected a protein-depleted dog from injury by an otherwise fatal chloroform anesthesia. However, a large amount of glycine, a simple amino acid, given before the anesthesia failed to confer any protection.

Messinger and Hawkins (2) found that diets rich in carbohydrate or protein protected dogs against injury to the liver by arsphenamine. The protective value of carbohydrate was less than that of protein. A diet high in fat increased the susceptibility of the liver to arsphenamine hepatitis.

Goldschmidt et al. (3) demonstrated that animals maintained on a high protein diet had a lower incidence of hepatic cellular necrosis following chloroform anesthesia. They found that the incidence and severity of damage to hepatic cells from chloroform anesthesia increased progressively with an increase in the concentration of the lipids in the liver. This relationship between chloroform damage and hepatic lipid concentration could be influenced by feeding protein, but was independent of the glycogen content of the liver. They believe that a diet high in carbohydrate may protect the liver either by reducing its lipid content or, in inanition, by sparing protein.

Miller, Ross and Whipple (4) demonstrated that the sulphur-containing amino acids, methionine and cystine are the specific factors responsible for the protective action of protein. Of the two, methionine affords much greater protection against the injurious effects of chloroform on the livers of protein-depleted dogs.

Quite recently Goodell, Hanson and Hawkins have reported the fact that methionine exerts a similar protective action against the hepatotoxic effects of arsphenamine.

Beattie, Herbert and Wechtel administered methionine therapeutically to a patient poisoned with carbon tetrachloride. Although it would be hard to say what the course would have been had the methionine not been given, certainly their patient made a more uneventful recovery than could have been expected. In spite of the ingestion and apparent absorption of 30 to 40 c.c. of carbon tetrachloride, no jaundice developed. The negative sulphur balance usually present in carbon tetrachloride poisoning was absent.

Many clinical conditions are characterized by protein depletion. Among these are fasting, repeated vomiting, gastrointestinal disturbances, hemorrhage, dietary limitations, chronic infection, hepatic cirrhosis, burns and chronic alcoholism - to mention only a few. To such patients the administration of potentially hepatotoxic drugs such as the organic arsenic compounds and the sulfonamides - as well as chloroform and atophan (cincophen) - may offer more than the usual hazards. Such patients should theoretically have less hepatic resistance to the virus of epidemic hepatitis. Every attempt should be made prior to or, if necessary, during the administration of drugs that may damage the liver or during an episode of epidemic hepatitis, to build up the protein stores. An enzymatic protein digest such as Amigen provides an excellent source of the sulphur-containing amino acids. Methionine therapy in acute poisoning (as by carbon tetrachloride) in the non-protein-depleted patient deserves a wider trial.

BIBLIOGRAPHY:

1. Miller and Whipple; Am. J. M. Sci., Feb. '40.
2. Messinger and Hawkins; Am. J. M. Sci., Feb. '40.
3. Goldschmidt, Vars and Ravdin; J. Clin. Invest., May '39.
4. Miller, Ross and Whipple; Am. J. M. Sci., Dec. '40.

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Early Activity After Surgery: A paper by Dr. J. H. Powers presented in the Bumed News Letter of May 26, 1944, submitted evidence indicating that the bed-stay of postoperative patients may be shortened with safety and that

such shortening accomplishes a significant reduction in the length of hospital stay and convalescence. This paper was first presented at a meeting of the Committee on Convalescence and Rehabilitation of the National Research Council on March 17, 1944. At that meeting a resolution was formulated suggesting that the armed services institute controlled comparisons of the effect of traditional postoperative treatment and regimes involving early ambulation. The suggestion was then referred to the Committee on Surgery for comment.

At the meeting of this Committee held on May 8, 1944, the suggestions of the Committee on Convalescence and Rehabilitation were reviewed following complete discussion of the principles involved. The Committee on Surgery unanimously adopted the following resolution:

"That a recommendation be sent to the Surgeons General of the Army and Navy that early ambulation in routine clean surgical cases be encouraged providing non-absorbable sutures are used."

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Arsenical Detoxifying Agent (BAL) Now 10 Per Cent Instead of 5 Per Cent: The Arsenical Detoxifying Agent to be used in the treatment of untoward reactions in the arsenotherapy of syphilis, which formerly was supplied in 5 per cent solution, is now being issued in 10 per cent solution. The dosage must be revised accordingly. All material forwarded by the Bureau in response to requests will be plainly marked, and detailed instructions, including recommended dosages, will accompany each unit of 10 ampoules. As stated in the Bumed News Letter of May 12, 1944, a supply is maintained at the following stations:

Bureau of Medicine and Surgery
Naval Hospital, Navy #10, F.P.O., San Francisco, Calif.
Fleet Hospital #105, F.P.O., San Francisco, Calif.
Naval Medical Supply Depot, Oakland, Calif.
Medical Supply Storehouse #10, Navy #120, F.P.O., New York, N. Y.

Supplies of the formerly-issued 5 per cent solution already on hand remain efficacious and need not be replaced. The instructions issued with either the 5 per cent solution or the new 10 per cent solution are correct as to dosage and should be followed.

The material is put up in a 10 per cent solution in peanut oil, containing 20 per cent benzyl benzoate as a solubilizing agent. The recommended dosage is 2.5 mg/kg (or 0.025 c.c./kg) repeated four times at four-hour intervals during the first day, and once daily for the following six days. In desperately ill patients two injections daily may be given after the first day at eight-hour intervals. The individual dose when adjusted to the body weight approximates the following:

Patient's Weight	Dose in C.C.'s
120-140	1.50
141-170	1.75
171-200	2.00

Cases of dermatitis may relapse when treatment is discontinued; such relapses may usually be controlled by one or two injections daily at the same dosage level, for 5 to 7 days.

At the dosage level recommended above, minor toxic reactions have occurred following less than 1 per cent of injections. An occasional patient may complain of nausea; there may be generalized aches and pains, or a burning sensation in the mouth or eyes. Rarely, there is a sense of constriction in the throat or chest. These symptoms are transitory, and have regularly disappeared within 30 to 60 minutes. No cumulative toxicity has been noted on repeated injections at four-hour intervals.

A total of 61 cases of various serious arsenical reactions have so far been treated, with highly satisfactory results in patients with toxic encephalopathy or arsenical dermatitis, inconclusive efficacy in blood dyscrasias and probably no demonstrable effect in the cases of so-called arsenical jaundice. In addition to these indications for the use of this material, it should also be given in sudden febrile reactions, exceeding 104°F., that develop within 12 hours after administration of an arsenical and persist for more than 24 hours.

It is further emphasized that the administration of this material destroys the therapeutic effect of the arsenical administered within the preceding 12 hours. (W.H.S.)

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Control of Fungus Infections of the Feet: At a conference on Fungus Infections of the Skin, held by the Division of Medical Sciences, National Research Council, on June 20, 1944, the following recommendations were made in response to a request by Colonel Lundeberg, of the Office of the Surgeon General, U. S. Army, for suggestions as to the need for foot baths and shoe sterilization:

1. Foot baths for the prevention of "athlete's foot" are not prophylactic, not necessary, and their use should be discontinued by the Army.

2. Shoe sterilization:

a. For factory rebuilt shoes: Sterilization is desirable, at least until further information is available.

b. For shoes turned in for exchange but not requiring repair: There is not sufficient evidence that such shoes transmit fungus infection of the feet to warrant sterilization.

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Gas Gangrene: Studies in experimental clostridial infections in animals and clinical reports from the various theatres of war permit one to make certain statements with respect to the prophylaxis and treatment of gas gangrene.

In the prevention of clostridial myositis nothing can rival in importance adequate surgery with excision of all devitalized muscle. Sulfadiazine administered orally or parenterally and continued in amounts sufficient to maintain an adequate blood level has proved to be a valuable prophylactic measure in infections caused by the Cl. welchii (perfringens) and the Cl. septicum (vibrion septique). It is apparently ineffective against the Cl. novyi (Cl. oedematiens). The trivalent gas gangrene antitoxin now available from the Supply Depot, when given early in adequate amounts, is effective against all of the above-mentioned organisms.

With respect to treatment in well-established cases, penicillin offers the greatest promise and should be used wherever available. The sulfonamides have little effect therapeutically and should be relied upon only when penicillin cannot be obtained. Both clinical reports and the results of animal experimentation provide evidence of the therapeutic value of the antitoxin, which should be given after appropriate tests for hypersensitivity, early, in adequate doses and repeatedly.

Combined therapy with all of the three agents mentioned is indicated. They seem to have additive or synergistic effect.

Adequate surgical care should not be neglected. In the presence of an adequate circulation of the affected part, conservatism should dictate the extent of surgical intervention. Often careful cleansing and adequate drainage will be sufficient surgery.

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The Supply Catalog now lists two Gas Gangrene Antitoxins:

Stock No.	Item	Unit
S1-1000	GAS GANGRENE ANTITOXIN, COMBINED, refined and concentrated; 1 therapeutic dose in syringe, contains 10,000 Cl. welchii, and 10,000 units Cl. oedematis-maligni antitoxins.	syringe

Stock No.	Item	Unit
S1-1001	GAS GANGRENE ANTITOXIN, TRIVALENT, refined and concentrated; 1 therapeutic dose in vial, contains 10,000 units of Cl. welchii (perfringens), 10,000 units of Cl. septique (vibrion septique), and 1,500 units of Cl. novyi (oedematiens) antitoxins.	vial

Wherever infection with Cl. novyi is a possibility, the trivalent antitoxin should be used, particularly in view of the resistance of this organism to the action of the sulfonamides.

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Catheterization of the Renal Vein: In their studies on the circulation in shock, Richards, Cournand and their co-workers (Columbia) have made much use of a technic whereby a catheter is inserted into an antecubital vein far enough so that its tip reaches the right auricle. With the catheter in place it is possible to make determinations of the intra-auricular pressure and chemical analyses of blood taken directly from the auricle.

Warren and others (Atlanta) have found that by properly angulating the tip and pushing the catheter still farther it can be made to enter the hepatic or renal vein. The possibilities opened up by this technic with respect to the study of renal and hepatic chemico-physiology are great. (Warren et al., Report to the American Society of Clinical Investigation, Atlantic City, May 8, '44.)

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Preservation of Blood Containing Carbon Monoxide for Transportation from the Field to the Laboratory: Blood treated with an anticoagulant (heparin or oxalate), collected under mineral oil and kept in tightly stoppered tubes, may be stored at room temperature for approximately one month and may be shipped from the field to laboratories without appreciable loss in carbon monoxide.

Because of the lack of skilled technicians and convenient apparatus, carbon monoxide determinations on blood are not conveniently performed in the field, and central laboratories are frequently called upon to analyze blood samples for carbon monoxide from distant stations after a considerable time has elapsed. If the blood samples are not properly prepared for shipping, the results of analysis may be worthless.

Therefore, investigations were carried out at the Naval Medical Research Institute to determine methods for the proper handling and transport of blood

for subsequent laboratory analysis, and the following technic was found to be satisfactory:

The blood is delivered into a test tube containing an anticoagulant* and overlaid with a few centimeters of mineral oil. After stirring the anticoagulant into the blood for several minutes with a glass rod, the rod is removed and the test tube filled to overflowing with mineral oil. A one-hole stopper is then inserted and forced into the test tube until some of the excess oil emerges through the opening in the stopper. While maintaining pressure on the stopper, a tight-fitting plug, most conveniently a piece of glass rod one inch long, is forced into the hole of the stopper. This procedure prevents contamination with air during transit, whatever the position of the tube.

*One drop (1/15 c.c.) of a solution of heparin (containing 10 mg. or 1100 "Toronto Units" per c.c.) made up to 15 c.c. with 0.85 per cent NaCl. prevents 5 c.c. of blood from clotting. A similar size drop of a saturated solution of lithium oxalate or of a 20 per cent solution of potassium oxalate may be used. The order of preference is heparin, lithium oxalate, potassium oxalate. (Research Project, N.M.R.I. - 69.)

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Water-Borne Tularemia in Western Canada: Bow and Brown again call attention to the fact, first pointed out in Russia by Karpoff and Antonoff in 1936, that sheep, rabbits, ground squirrels, field mice, beavers, etc., infected with tularemia may contaminate water supplies and so spread tularemia to human beings. (Canad. M.A.J., Jan. '44.)

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Use and Care of Intravenous Equipment: It is desirable to bring to the attention of medical officers the fact that the equipment for intravenous administration contained in Standard Army and Navy Plasma Packages (Fig. 1) can be used with all other Army and Navy intravenous solutions. These are supplied by three companies in bottles designed to deliver their contents through either the set supplied by the manufacturer or the standard Army-Navy plasma equipment.

Adaptation to the different bottles is shown in Figs. 2 through 6. The procedure in using an Upjohn bottle is identical with that for plasma. Airway and delivery needles are inserted through the small diaphragms (Fig. 2A c, e). The Baxter and Schering and Glatz bottles contain glass airway tubes. These function with either a plasma airway as shown (Figs. 3 and 4) or with only a needle inserted through the diaphragm covering the glass tube (Figs. 3B and 4B). The commercial sets connect with the bottle through glass adapters rather than needles. These are inserted through the appropriate diaphragms after the latter have been punctured with a sterile needle (Figs. 2A d, 3A, 4A j).

Amigen solutions for parenteral administration may readily be prepared from the powder and can then be administered with any of the equipment illustrated in Figs. 1, 2, 3 and 4. (See Form Letter, page 26.)

The liter flasks, in which the 5% Amigen - 5% Dextrose solutions are supplied by Mead Johnson and Company, have a rubber closure adapted for use with the tubing and needles supplied with the standard Army and Navy plasma packages and standard intravenous equipment as shown in Figs. 5 and 6. Reference to these illustrations will show that the procedure in using the Mead Johnson and Company bottle is identical with that for the plasma and the Upjohn bottles.

As each package of plasma contains complete sterile intravenous equipment, the administration of several bottles of plasma in succession to one patient through the same set will provide excess sterile sets of tubing and needles which can be used as described. It is quite important to point out, however, that merely because the cellophane wraps appear to be intact at each end of the tubing, sterility is not maintained indefinitely after removal from the cans. Only those sets which have been recently removed or carefully stored after removal from plasma cans should be used without resterilization.

Intravenous equipment through which plasma or crystalloids have been administered may be used several times if properly cleaned. Such sets should be taken apart and flushed out with large amounts of tap water under pressure immediately after use. Rinsing three times with freshly distilled pyrogen-free water using a total of one liter for each 30 to 40 inch piece of tubing, drying and autoclaving within two hours of rinsing should provide pyrogen-free equipment.

If there is any delay between using the set and flushing it out, extra precautions are necessary. If possible, take the set apart and leave it soaking in water until it can be cleaned. At the earliest opportunity flush out the set with tap water under pressure, removing all hardened particles of blood or plasma. Place in 5 per cent sodium carbonate, 5 per cent sodium hydroxide, or 3 per cent sodium phosphate solution and keep for 15 minutes at a bubbling boil. Remove, wash thoroughly to remove alkali and carefully clean inside by flushing for 10 to 15 minutes with running tap water under pressure. Rinse three times with freshly distilled pyrogen-free water using a liter for each 30 to 40 inch piece of tubing. Drain any excess water or saline solution from the tubing, assemble with the prepared glass and needle parts and sterilize immediately, certainly before the elapse of two hours after cleaning and assembly. For any equipment which might be used with whole blood, the final rinsing should be done with pyrogen-free normal saline solution instead of distilled water to avoid hemolysis. When re-assembling a plasma set for use

with crystalloids or Amigen, the filter may be omitted and the long delivery tube attached directly to the short needle connector.

The glassware parts of a used intravenous assembly are cleaned by rinsing three times in tap water. Rinse with chromic acid cleaning fluid, then rinse six times with tap water. Finally rinse twice with pyrogen-free distilled water or pyrogen-free normal saline solution. Drain with mouth down before assembly.

Formula for Chromic Acid Cleaning Fluid (glassware only):

Potassium dichromate (technical crystals)	1 part
Sulphuric acid, concentrated	1 part
Distilled water	10 parts

New or used needles for intravenous use are prepared by washing inside and out with a solution of green soap and 5 per cent phenol. Clean the hilts with a cotton applicator. Rinse three times with 70 per cent alcohol. Needles to be attached to the intravenous set are directly assembled. Unattached needles are placed in a convenient type of needle case and sterilized. Sharpen all needles before placing them in line for use.

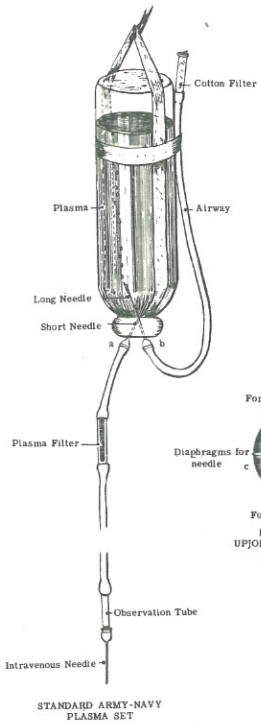
The steel filters used in a standard plasma set are cleaned by flushing with tap water under pressure until all obvious particles are washed off. Soak with filters in a 5 per cent aqueous solution of nitric acid for thirty minutes. Wash thoroughly with tap water under pressure and finally rinse at least three times with pyrogen-free distilled water.

The sterilization of intravenous equipment by steam under pressure is done at 240 to 250°F. (15 pounds pressure) for 15 minutes, the timing to begin when the sterilizer indicates required heat and pressure. All material removed from an autoclave must be well dried. Wet and soggy articles are to be considered unsterile. Sterilization may be accomplished in a dry heat oven. The operation is carried out at 320°F. for one hour.

Intravenous equipment must be assembled in such a manner that sterilizing air and steam can circulate throughout all inside surfaces. The needle and glass ends must be well covered and secured with paper, plastics, etc., but must not be sealed shut at either end. Rubber tubing or an assembled intravenous set should be loosely coiled or placed vertically in the sterilizer to prevent kinking and collapse. Rubber tubing should not touch metal surfaces in sterilizers nor should it be placed on uncovered and cold surfaces when removed from the sterilizer.

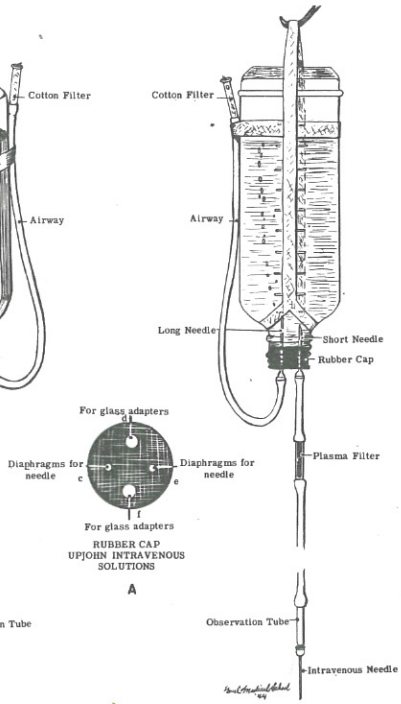
Unless adequate facilities are available for storage of sterile supplies, no intravenous equipment should be used more than 48 hours after sterilization.

DIAGRAMS SHOWING HOW THE INTRAVENOUS EQUIPMENT CONTAINED IN THE STANDARD ARMY-NAVY PACKAGE OF DRIED PLASMA MAY BE USED WITH OTHER ARMY AND NAVY INTRAVENOUS SOLUTIONS.



STANDARD ARMY-NAVY PLASMA SET

FIG. 1

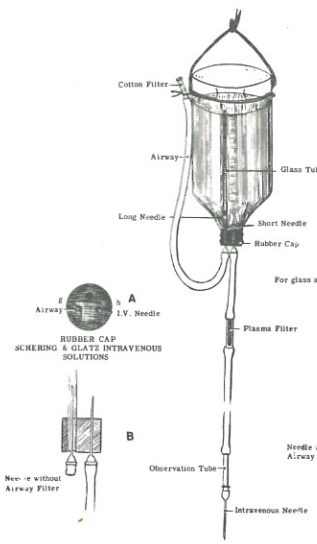


UPJOHN SOLUTION BOTTLE

FIG.2

RUBBER CAP UPJOHN INTRAVENOUS SOLUTIONS

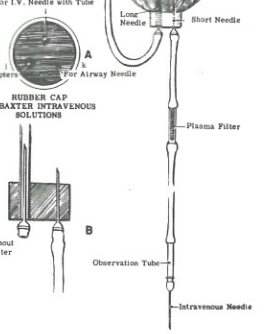
A



SCHERING & GLATZ SOLUTION BOTTLE

FIG. 3

RUBBER CAP SCHERING & GLATZ INTRAVENOUS SOLUTIONS



RUBBER CAP BAXTER INTRAVENOUS SOLUTIONS

BAXTER SOLUTION BOTTLE

FIG.4

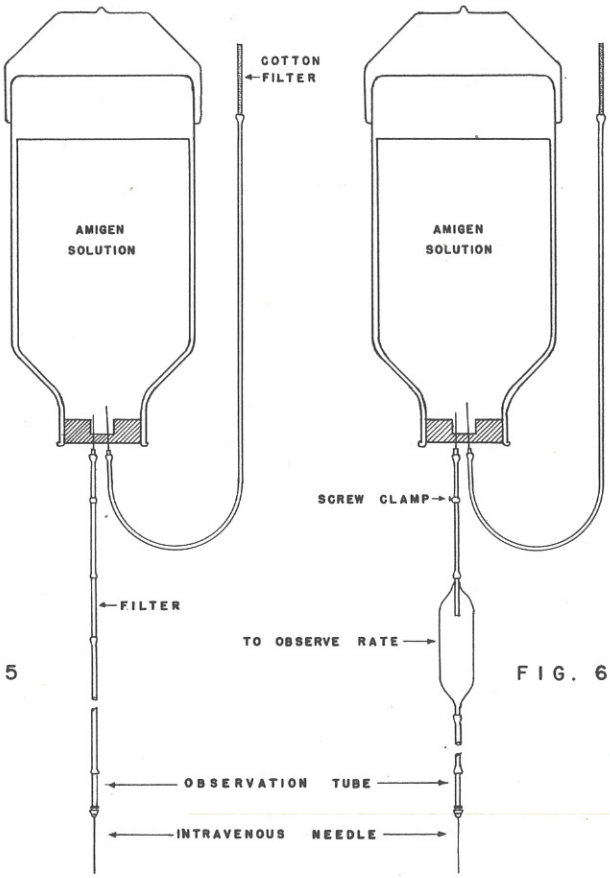


FIG. 5

FIG. 6

For information regarding other salvage from plasma sets (e.g., re-use of the distilled water bottles), refer to the article by Newhouser and Lozner, "Suggestions on the Use of the Equipment of the Standard Army-Navy Package of Dried Plasma for Whole Blood Transfusion", U. S. Naval Medical Bulletin XLII:451-6, Feb. '44. (L.R.N.; S.T.G.; H.R.E.)

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Dental Laboratory Gas Generator: Leaded Gasoline Must Not Be Used in Gasoline Gas Stock No. S12-075 Generator Outfit: The subject outfit is made by the Buffalo Dental Manufacturing Company and consists of (a) Generator, (b) Blowpipe, (c) Blowpipe Stand, (d) Case Heater, (e) Rubber connecting tubing, reducer and "Y" connection, and (f) Foot blower of the bellows type. This set is for overseas use where other fuel is not available. Gasoline containing lead should not be used because of the danger of contaminating the gold alloy with a minute amount of lead which will cause the alloy to become extremely brittle. (R.S.D.)

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Medical Officers Who Speak Spanish or Portuguese: The Association of Military Surgeons will hold its next annual meeting in New York City, November 2, 3 and 4, 1944. It is requested that medical officers who speak Spanish or Portuguese and who attend make themselves known to the secretary when registering. Numbers of medical officers from Central and South America are expected.

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Tropical Medicine Meetings: The Southern Medical Association and the American Society of Tropical Medicine will hold a joint annual meeting in St. Louis, November 13-16, 1944. Also meeting at the same time and place will be the American Academy of Tropical Medicine and the National Malaria Society.

All reservations will be handled through the Hotel Committee of the St. Louis Medical Society, and the request for reservations should include not only the name but also the kind and price of accommodations desired and the expected date and time of arrival.

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Public Health Foreign Report:

Disease	Place	Date	Number of Cases
Cholera	India, Calcutta	Apr. 1-8, '44	34
		Apr. 15-22, '44	58
		Apr. 22-29, '44	95
		Apr. 29-May 6, '44	98
Plague	Egypt, Ismailiya	May 6-13, '44	39 (21 fatal)
		May 14-20, '44	49 (28 fatal)
	French West Africa - Dakar	May 13-20, '44	1
	India, Calcutta	Apr. 15-22, '44	2 (fatal)
	Madagascar	Jan. 20-Mar. 10, '44	50 (41 fatal)
	Peru	January '44	7 (4 fatal)
		February '44	7 (2 fatal)
		March '44	7 (1 fatal)
Smallpox	Bolivia	April '44	77 (12 fatal)
	Br. East Africa, Uganda	Apr. 8-15, '44	92
		Apr. 15-22, '44	171
	Fr. Equatorial Africa	February '44	137
		March '44	221 (36 fatal)
	India, Bombay	Apr. 15-22, '44	99 (42 fatal)
	Nigeria	Apr. 8-15, '44	55 (20 fatal)
		Apr. 15-22, '44	140 (21 fatal)
Yellow Fever	Belgian Congo, Leopoldville	Mar. 4-11, '44	1 (1 fatal)

(Pub. Health Rep., May 5, 12 & 19; June 2 & 9, '44.)

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To: All Medical Officers. P2-3/P3-1(012-41)
BUMED-Y-AFR

Subj: Malaria - Recommendations Concerning the Treatment of Clinical Malaria. 10 Jul 1944

1. Choice of drug: The three drugs which have been most widely used in the treatment of clinical malaria are atabrine, quinine and plasmochin.

a. Atabrine (Quinacrine hydrochloride, U.S.P.; Mepacrine in British usage): Evidence indicates that atabrine is as effective as quinine and in many respects is to be preferred. This fact and the critical shortage of quinine dictate the routine employment of atabrine. A clinical response slower than that obtained with quinine, which was formerly a disadvantage of atabrine, has been overcome by the employment of higher initial doses. Another former objection, the so-called toxicity of atabrine, has not been substantiated by wide experience. The toxicity of atabrine now appears to be less than that of quinine.

b. Quinine: A few indications which demand the use of quinine derivatives remain: atabrine may not be available, and rarely there is an individual who will show an intolerance to the drug. It is also generally agreed that quinine, intravenously, is preferable in patients critically ill with malaria, as it appears to be a less dangerous drug than atabrine administered intravenously and more rapidly acting than atabrine administered intramuscularly.

c. Plasmochin: This drug has been combined with quinine in the treatment of malaria or has been used to follow a course of atabrine. It is not efficacious as the sole drug for therapy. The toxic and therapeutically effective doses tend to coincide. Formerly its use was advised on the theory that it would reduce the relapse rate in P. vivax infections. Recent evidence discloses no appreciable effect in this regard. It has some action in the destruction of gametocytes, and consequently may be useful in reducing the spread of malaria. In certain cases, where gametocytes persist in the blood stream following the usual treatment with atabrine or quinine, the addition of a course of plasmochin may be useful in destroying these sexual forms.

2. Laboratory diagnosis: Where competent film examination of the blood is possible, it is inexcusable to start specific chemotherapy without a positive laboratory diagnosis. The urgently ill case in which no delay can be safely permitted is an exception. The habitual employment of atabrine or quinine in all fevers occurring in a malarious area without prior demonstration of the Plasmodium is a dangerous practice which on occasion will result in the death of a patient. A negative thick film casts doubt upon the diagnosis of malaria and should lead to close observation to determine if the fever is of other than malarial etiology. Occasional cases with negative smears, however, may be dangerously ill with malaria.

a. Under combat conditions, or in other situations where laboratory facilities are lacking, it may become necessary to treat patients without confirmation of the diagnosis by blood smear. Keen observation then becomes essential so as not to miss the occasional case of meningitis, pneumonia or other febrile disease which may simulate and mistakenly be assumed to be malaria.

b. Importance of species diagnosis: Where possible, in addition to parasite diagnosis, species diagnosis should be attempted. A diagnosis of P. falciparum infection will dictate close observation of the patient for the onset of pernicious symptoms; furthermore, relapse may be predicted as being unlikely. In contrast, a patient with a P. vivax infection is less likely to develop critical symptoms, but is apt to have repeated relapses over a prolonged period.

c. Verification of technical proficiency: It is important to note that the accurate diagnosis of malaria by either thin or thick film technic requires prolonged experience, particularly in the case of the thick film technic. False-positive diagnoses in which blood platelets are mistaken for Plasmodia are the most common errors. Technicians should be required to check continuously with other competent laboratories to determine the reliability of their own work.

3. Drug intolerance and toxic manifestations in the use of atabrine, quinine and plasmochin: Each of these drugs may give rise to untoward symptoms in occasional individuals. Severe reactions are most common with plasmochin.

a. Atabrine: Toxic symptoms of any type, attributable to atabrine, are unusual in the treatment of clinical malaria. Symptoms of nausea, vomiting, diarrhea, abdominal cramps and headache have been reported in some normal individuals when first taking atabrine for suppressive treatment. These symptoms are uncommon when the drug is administered for the treatment of a clinical attack and are more apt to be due to malaria than to the drug. Mild excitement has occasionally been ascribed to the effect of atabrine; rarely, there have been reported acute maniacal psychoses which subsided on withdrawal of the drug and recurred on readministration. Occasionally urticarial and scarlatiniform rashes, and rarely exfoliative skin reactions, have been reported. The etiological relationship of atabrine with these toxic manifestations has not always been conclusively demonstrated. While it is well to appreciate the toxic possibilities, experience with the drug will, in the vast majority of cases, tend to emphasize its relative nontoxicity. Exceeding the recommended dosage, however, may lead to toxic effects. The drug is a yellow dye, and the occurrence of a yellow skin deposit in most cases should not be interpreted as a toxic manifestation.

b. Quinine: In the great majority of patients the administration of quinine leads to few untoward effects. Effective therapeutic dosage, however, is usually

accompanied to a variable degree in almost every patient by one or more of the following symptoms of cinchonism: tinnitus, nausea, gastric distress, dizziness, temporary deafness, tremors and palpitation. These milder symptoms indicate adequate blood levels for favorable therapeutic action but are quite objectionable to many patients.

More rarely severe untoward reactions occur which are definitely ascribable to quinine. These are generally allergic in nature. Suspicion also points to quinine as an important precipitating factor in blackwater fever. Prolonged use of quinine has been reported as a cause of permanent impairment of hearing.

c. Plasmochin: Effective doses of this drug frequently lead to toxic manifestations. Symptoms include abdominal pain (which may be severe enough to require morphine), nausea, vomiting, headache, dizziness and drowsiness. Acute yellow atrophy of the liver, jaundice, cyanosis, circulatory collapse and hemoglobinuria are the more rare and exceedingly dangerous effects of the drug.

4. Recommended treatment for clinical malaria:

a. Uncomplicated malaria (patients able to retain oral medication) and parasitemia without symptoms: Atabrine dihydrochloride 0.2 Gm. (3 grains) is given orally every six hours night and day for five doses; followed by 0.1 Gm. (1-1/2 grains) three times daily after meals for six days (total of 2.8 Gm. in seven days).

b. Malaria complicated by vomiting (patients unable to retain oral medication): Atabrine dihydrochloride 0.2 Gm. (3 grains) in 5 c.c. sterile distilled water is injected intramuscularly with the usual precautions into each buttock (total 0.4 Gm. or 6 grains). If necessary, one or two additional doses of 0.2 Gm. (3 grains) may be given intramuscularly at intervals of six to eight hours. As soon as the patient can take and retain oral medication, atabrine should be given by mouth in such dosage as to give a total by both routes of 1.3 Gm. in forty-eight hours, followed by 0.1 Gm. three times a day after meals for five days (total 2.8 Gm. in seven days). Intramuscular atabrine might well be used where serious illness threatens or where malaria is complicated by other diseases. A maximum blood concentration of the drug is obtained about one hour after the intramuscular injection.

c. Malaria complicated by coma or impending coma, or by high parasite blood film density (P. falciparum infections), even when patient does not appear critically ill (par. 7c(2)): Quinine dihydrochloride 0.6 Gm. (grains 10) in 300-400 c.c. of sterile physiological saline is injected very slowly intravenously. This treatment may be repeated in six or eight hours if required, but it will be better to anticipate the need by giving intramuscular atabrine immediately following the intravenous quinine. Quinine given intravenously is eliminated in

about three hours. When the patient can take and retain oral medication, a complete course of atabrine should be given as described above for uncomplicated malaria.

5. Alternative treatment schedules: The drug routine recommended in paragraph 4 will be effective in the vast majority of cases. In the past, in the hope of lessening the number of relapses, almost every conceivable variation of these methods has been attempted. These variations have embraced increased dosage and prolongation of administration of various drugs, singly or in combination, all without appreciable increase in therapeutic efficacy. Deviation from the recommended schedules therefore should be only for the purpose of meeting specific individual needs. The routine use of quinine is specifically prohibited by directive, and is to be employed only when atabrine is not available, when there is a serious intolerance to atabrine, or when a change in medication is deemed advisable owing to repeated relapses following atabrine therapy.

a. Quinine by mouth: The sulfate or the hydrochloride (the latter is more readily absorbed) should be given in doses of 1 Gm. (15 grains) by mouth after meals three times daily for two days followed by 0.6 Gm. (10 grains) t.i.d. for five days.

b. Quinine intramuscularly: Quinine dihydrochloride, 1 Gm. (15 grains), is given in 10 c.c. of sterile physiological saline. Sterile technic should be scrupulous, the injection being made into the buttock, care being taken to avoid the large nerves and vessels. The area of injection should be massaged for two or more minutes. Intramuscular quinine has gained a reputation as being dangerous owing to abscess formation. However, its routine use without ill effects has also been reported. Oral medication should be resumed as soon as possible.

c. Plasmochin: (see indications in paragraph 1 (c)): The drug may be given concurrently with quinine or immediately following atabrine but, because of additive toxic effect, never with atabrine. It is given in doses of 0.01 Gm. (1/6 grain) by mouth t.i.d. after meals for four days. The drug should be administered under careful medical supervision. It should not be given to debilitated patients. Each dose should be accompanied by at least 1 Gm. of sodium bicarbonate. Toxic symptoms of various degrees are apt to occur in the above dosage; the occurrence of any toxic symptom requires that the drug be discontinued promptly.

6. General care:

a. Keep the patient in bed in screened ward or under a mosquito net and maintain fluid intake at 3 to 4 liters daily. If necessary, fluids should be given intravenously. Sweetened tea and fruit juices are usually well accepted by the patient. If sweating leads to considerable fluid loss, the chloride level should be maintained with salt administration. Hot water bags and blankets should be

used during the chill; cold sponges and packs are indicated when fever is high. Antipyretics are contraindicated since they tend to mask the true nature of the patient's condition. When sedatives are required, judicious use should be made of the barbiturates.

b. When nausea or vomiting is present, stop the intake of solid food, particularly when a paroxysm of fever is expected. Give sips of alkaline water. If vomiting becomes frequent, administer glucose intravenously, using a 5 per cent solution in physiological saline. One milligram of thiamine hydrochloride for each 25 grams of glucose should supplement glucose administration.

c. Convalescence from uncomplicated single attacks of malaria is usually rapid. Such patients should not be kept in the hospital an undue length of time. Patients who have had many attacks of malaria, especially when the intervening intervals are short, may remain for an excessively long time in a debilitated and depressed state. Patients who have injuries or other diseases often fall in this group. In such cases, full use should be made of available measures to hasten recovery including:

(1) Diets which are liberal and well planned both as to vitamin and nutritive value and as to attractiveness and palatability.
(2) Vitamin supplements.
(3) Iron replacement, if anemia is present (ferrous sulfate 0.6 Gm. (10 grains) three times a day after meals).
(4) Physical therapy in suitable forms.
(5) Adequate rest and sleep, with judicious use of sedatives.
(6) Where feasible, the patient should enter a reconditioning program as soon as possible.

7. Practical points in the management of malaria:

a. Pertaining to diagnosis:

(1) Suspect malaria regardless of admission diagnosis. It is a cardinal point that where the possibility of malaria exists, the diagnosis of malaria should be considered on every admission even if the symptoms and signs may at first appear to be unrelated to malaria. Malaria is apt to manifest itself in many guises. Fever is not always present; indeed, a patient critically ill with the disease may have a subnormal temperature.

(2) Importance of laboratory confirmation of clinical diagnosis. Repeated thick films should be studied by competent technicians in every case in which the diagnosis of malaria is a possibility. Most authorities agree that over 90 per cent of patients with malaria will, with competent examination, show malaria parasites on the first or second film examination, provided the patient has not recently been under antimalarial treatment. The symptoms and signs of a patient repeatedly showing negative thick films are almost surely not due to malaria.

(3) Significance of clinical response to specific therapy. Where a clinical diagnosis of malaria has not been confirmed by laboratory examination, favorable response to antimalarial drugs does not prove that the fever was of malarial origin. On the other hand, failure of response (when it can be assured that the patient has taken and has absorbed the drug) is an almost positive indication that the case is not of malarial etiology.

b. On the prior use of suppressive treatment:

(1) Parasitemia in hospital admissions (irrespective of admission diagnosis). In certain highly endemic areas as many as 95 per cent of the men exposed develop latent malaria while on atabrine-suppression regimes. Thus when atabrine is stopped during hospitalization for any cause, a parasitemia, often accompanied by clinical symptoms, is apt to develop and to confuse the true condition. The finding of parasites in the blood of such patients may be unassociated with the complaints for which the patient was admitted. However, these patients should be treated as for clinical malaria (paragraph 4).

(2) Absence of parasite resistance in prolonged atabrine usage. Experience with atabrine indicates that the parasite does not develop a drug resistance following continued atabrine suppressive treatment. Patients "breaking through" atabrine suppression, even when suppression has been continued for prolonged periods, promptly respond to the doses recommended for the treatment of clinical malaria.

(3) Effect of suppressive treatment on the detection of parasites in clinical break-throughs. The employment of suppressive treatment prior to a clinical break-through does not appear to reduce appreciably the chance of demonstrating Plasmodia in thick films.

(4) Treatment in asymptomatic parasite-positive cases. Individuals who have been under suppressive treatment may show parasites and yet present no clinical evidence of malaria. In such cases the patient should receive the same course of chemotherapy as the acute case.

(5) Factors precipitating clinical malaria from latency. Patients ill from other causes who have been on suppressive treatment are especially apt to come down with clinical symptoms of malaria. Surgical operations, trauma and shock are particularly apt to precipitate clinical attacks. Patients likely to have latent malaria should promptly be given full therapeutic treatment when malaria is superimposed upon another condition.

c. In P. falciparum infections:

(1) Rapid development of critical symptoms. The very sudden onset of pernicious symptoms in malignant tertian malaria is sufficiently common to require very close observation of patients with this type of malaria. The

presenting symptoms in P. falciparum infections may be of a very acute nature. Patients who a few hours previously appeared well may be admitted in coma or in convulsions; hyperpyrexia or a subnormal temperature may be present. In the critical cases the condition of the patient usually requires that intravenous therapy be immediately instituted without waiting for laboratory confirmation of the diagnosis.

(2) High parasite densities in P. falciparum infections. When the proportion of red cells infected with Plasmodia exceeds a ratio of 1 in 20, a critical condition of the patient is impending, if not already present, and energetic specific therapy is indicated. Usually, intravenous medication should be given at once.

(3) In cerebral malaria. Lumbar puncture is indicated as a therapeutic adjunct in cerebral malaria. The spinal fluid should be drained off until the pressure is normal or even subnormal.

d. Pertaining to treatment in special circumstances:

(1) Species differences; relapse vs. primary case. The treatment recommended above is in general satisfactory, regardless of the species of Plasmodia, whether the case is a primary infection or a relapse.

(2) Parasitemia without clinical evidence. These cases should receive the same treatment as those patients with uncomplicated clinical malaria.

(3) Interval treatment in the absence of parasitemia or clinical manifestations. There is no evidence that repeated courses of therapy as recommended for the clinical attack when given during asymptomatic intervals is of any benefit. Continuous suppressive therapy, however, may be indicated when the patient suffers frequent relapses with marked debilitation.

(4) Failure of clinical response in laboratory-confirmed cases of malaria. Patients who show either clinical or parasitic relapse during or shortly after a full course of atabrine therapy should be carefully studied to see that they are actually taking the prescribed dosage. When failure to take the drug can be ruled out, poor absorption is the probable explanation. The intramuscular administration of atabrine may then be resorted to, or a change to quinine may be tried. (See paragraph 5.)

8. Postmortem examination: When a death is presumably due to malaria, certain procedures are indicated for confirmation of the cause of death:

a. A careful description of the gross appearance of the liver, spleen and brain should be recorded. Sections of these organs, accompanied by complete history of suppressive treatment and clinical course, should be forwarded whenever possible to the Naval Medical School, Bethesda, Maryland.

b. More important, smear preparations should be made of the bone marrow, splenic pulp and brain tissue. These preparations must not be too thick, and tissue must be teased out into a thin layer.

c. All smear preparations should be fixed with methyl alcohol and stained with Giemsa. Tissue for sectioning should be cut into blocks 1 cm. in diameter, fixed with Zenker's solution for 8 to 10 hours, washed in several changes of water or in running water for about six hours, and then be preserved in 70 per cent ethyl alcohol to which tr. iodine has been added in sufficient amount to tint the solution a straw color.

9. Note on the course of malaria: Falciparum infections, in comparison with vivax malaria, have relatively little tendency to relapse. Vivax infections relapse as time goes on in a decreasing proportion of the original group. Whereas second attacks may occur in 60 per cent of those infected, tenth attacks probably affect only 1 per cent or less. The interval between attacks tends to be about four weeks, but may be shorter or much longer. In general, later attacks tend to be briefer and milder than early attacks, but there are many exceptions. No criterion of cure is available. As a rough approximation, it may be said that when six months have passed without an attack, the patient not taking suppressive therapy during that time, the further occurrence of numerous relapses is unlikely. Attacks after two to three years are believed to be unusual.

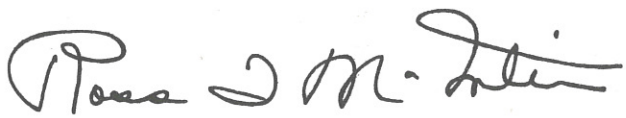
10. Note on the action of atabrine and quinine:

a. Absorption and plasma level: Both of these drugs are rapidly absorbed from the gastrointestinal tract; under ordinary conditions the rates of absorption are not significantly different. Their efficacy is dependent upon their concentration in the circulating blood plasma. The effective plasma level of atabrine is very much lower than that of quinine. Quinine is taken up by the tissues to a smaller extent than atabrine, and effective quinine plasma concentrations, therefore, are usually attained promptly. Atabrine at first is taken up to a much greater extent by the tissues, so that effective levels in the plasma are reached only as certain tissues become more or less saturated. The method of administering atabrine which is recommended in par. 4a above, includes the administration of a relatively large amount in the first 24 hours which acts as a "loading" or "priming" dose. By this means a therapeutic effect is secured as rapidly with atabrine as with quinine when both drugs are given by mouth. This method has been used extensively and has proved to be highly satisfactory in the treatment of the vast majority of acute attacks.

b. Duration of effect: Any quinine given orally is, for practical purposes, completely eliminated in 48 hours. After a therapeutic course of atabrine, elimination of the drug may not be complete for several weeks. During the latter part of this time, however, the plasma level is far below the threshold

of therapeutic efficacy. Nevertheless, an effective level is often maintained for at least three weeks. In this connection, it has been shown that the average interval between attacks is much longer following a course of atabrine than it is after quinine.

c. Relation to the parasite: Available evidence shows that atabrine cures falciparum infections. Whether or not quinine also does is uncertain. Both atabrine and quinine rapidly bring about the destruction of vivax trophozoites. Neither of these drugs can be shown to have any influence on the probability of subsequent relapses in vivax malaria. It would appear that a form of the vivax parasite, neither sporozoite nor trophozoite, which is not susceptible to atabrine or quinine, must exist. The persistence of such forms may be an explanation of the occurrence of vivax relapses.



ROSS T McINTIRE
Vice Admiral (MC), USN
Chief of Bureau

To: All Medical Officers. L4-2/JJ57(032)
BUMED-X-AE-III

Subj: Letter of Information and Instruction on the Use of Casein Hydrolysate (Amigen). 3 Jul 1944

Refs: (a) Bumed News Letter Item: Nutrition in Convalescence, Vol. 3, No. 3, p. 9.
(b) Bumed News Letter Item: Parenteral Protein Administration, Vol. 3, No. 5, p. 4.

1. Amigen has been added to the Supply Catalog as follows:

Stock No.	Item	Unit
S1-2465	Enzymatic Hydrolysate of Casein and Pork Pancreas (Amigen), powder (for parenteral use).	50-gm can
S1-2466	Enzymatic Hydrolysate of Casein and Pork Pancreas (Amigen), 5% in 5% Dextrose Solution, 1000 cc flask (for parenteral use).	6-in case

2. Amigen powder (S1-2465) is a stable product suitable for extracontinental shipment. The contents of a single can (50 Gm.) is the amount required to prepare 1,000 c.c. of a 5 per cent solution for parenteral administration. Solutions of varying concentration for oral feeding may also be prepared from the powder. A pilot allotment of one case (48 cans) of Amigen powder will be shipped from the Naval Medical Supply Depot, Brooklyn, N. Y., to all Naval Hospitals, Convalescent Hospitals, Fleet Hospitals, Base Hospitals and Hospital Ships. Subsequent procurement will be by requisition.

3. Amigen solution (5% Amigen - 5% Dextrose), in liter infusion flasks, is sterile and pyrogen-free, ready for immediate intravenous administration. This preparation is less stable, having a six-months' expiration dating. Therefore, distribution will be limited to Continental Hospitals and to those Extracontinental Hospitals where rapid transportation will assure arrival at destination in adequate time for use within expiration dating. One case (6 flasks) of Amigen solution will be shipped from the Naval Medical Supply Depot, Brooklyn, N. Y., to each Continental Hospital and to Extracontinental Hospitals where above-stated shipping conditions can be met. Subsequent procurement will be by requisition.

4. A leaflet prepared by the manufacturer describing Amigen, indications for its use and methods of preparation and administration of Amigen solutions accompanies each case unit.

5. Casein hydrolysate (Amigen) is a dried enzymatic digest of purified casein and pork pancreas. The product is made by a process of digestion of casein and pork pancreas in which the pancreatic enzymes convert casein and the proteins of the pancreas almost entirely to amino acids, a small amount remaining as simple peptides. The amino acids contained include the ten "essential" as well as certain non-essential amino acids.

6. Appropriate manufacture and laboratory control assure a product in powder form which is commercially sterile (The bacterial count is well below the pyrogenic level; hemolytic cocci and Esch. coli are absent.) and a product in solution (5% Amigen - 5% Dextrose) which is sterile and pyrogen-free. Appropriate testing of batches also assures a non-antigenic product capable of supporting growth in laboratory animals and having a metabolic value equivalent to orally ingested protein, as shown by comparative observations in nitrogen balance and plasma regeneration.

7. In a report of the Committee on Convalescence and Rehabilitation of the National Research Council on the "Nutritional Aspects of Convalescent Care" (ref. (a)), it was pointed out that solutions of hydrolysate of casein, or other high-grade proteins, represent a physiologically acceptable method of providing nitrogenous food parenterally. Following a survey of the various preparations available for parenteral protein feeding, the Committee reached the following conclusions:

"Transfusion of whole blood and infusion of normal or concentrated plasma are not ordinarily thought of as nutritional measures. They are used for maintaining blood volume and circulation. Every 100 c.c. of normal blood contains about 15 Gm. of hemoglobin and 6 Gm. of plasma protein. Hemoglobin is not suitable for replacement of tissue protein. However, injected plasma protein is metabolized to some extent and so provides a source of nitrogen nourishment and protects, in part at least, against tissue wastage.

"Solutions of hydrolysates of casein, or other high-grade proteins, have recently been employed and, because food protein is normally hydrolyzed before absorption, represent a more nearly physiological method of parenterally providing nitrogenous food. Of the various hydrolysates available there is only one which is well utilized and will maintain nitrogen equilibrium. It is prepared by enzymatic hydrolysis of casein. Acid hydrolysates should have certain theoretical advantages; however, up to the present time, it has been impossible to produce acid hydrolysates without destroying certain essential amino acids, notably tryptophane. Mixtures of pure amino acids suitable for injection have definite advantages, but they are expensive and are not yet available in large quantity."

8. The importance of a constant positive nitrogen balance in wound healing and in resistance to infection has been well established. This was emphasized in ref. (b), and the role of casein hydrolysate in meeting the large protein needs occurring in severe burns, wounds and infections was discussed.

9. The indications for use of Amigen in general include most cases usually recognized as requiring injections of dextrose and saline. The specific types of patients where the need is more direct and urgent may be grouped as follows:

a. Patients unable to take food by mouth: In this category are patients with gastrointestinal obstruction of any kind - from the mouth to the rectum. Such conditions include esophageal spasm or stricture, carcinoma of the esophagus, stomach or colon, pyloric or intestinal obstruction, intussusception, perforation of the intestine, diverticulitis of the colon, et cetera.

To such conditions may be added intractable vomiting, pyloric stenosis, or prolonged anorexia in which even tube feedings are not retained.

b. Patients who should not take food by mouth: In many patients the ingestion of food is deleterious, and the gastrointestinal tract is in need of complete rest. Frequently included in this group are cases with severe infection of the gastrointestinal tract, such as: generalized peritonitis, esophagitis, gastritis, gastroenteritis, ulcerative colitis, typhoid fever, severe diarrhea or dysentery. Included also in this category are all postoperative patients in whom an anastomosis or other surgical procedure is performed on the gastrointestinal tract. Battle casualties with perforated wounds of the abdomen, peritonitis, or those requiring subsequent extensive repair are necessarily included in this group.

c. Patients who cannot take sufficient food by mouth: In such cases it may be important to correct an existing deficiency more rapidly than is possible by the oral route alone. Patients who have suffered from exposure and malnutrition due to inadequate food supply, or those who have been sick and are severely malnourished because of the associated anorexia belong in this category. Others who are extremely malnourished and are unable to eat enough food to correct the deficiency in a reasonable period before operation likewise are benefited by Amigen. In nutritional edema, or in the presence of severe hypoproteinemia, parenteral administration of amino acids, in the form of Amigen, is indicated.

Patients with severe wounds and burns require large quantities of protein to correct their protein depletion. Furthermore, to maintain nitrogen balance essential to healing and tissue regeneration, it is necessary in these cases to continue a high level of protein intake because of excessive protein catabolism, protein loss in blood and exudates, and protein required for new tissue. These patients rarely can meet their large protein need by ingestion of food. By the

use of Amigen orally and parenterally the protein deficit may be rapidly corrected and nitrogen balance maintained.

Patients with high fever, and accompanying anorexia, likewise profit by supportive animo acid treatment with Amigen.

d. Patients who cannot assimilate protein: Acute infections may diminish the secretion of proteolytic enzymes. It is quite possible that much malnutrition, especially in infancy and in senility, is due not so much to inadequate food intake as to poor assimilation. In nutritional edema the gastrointestinal tract may become involved, leading to imperfect digestion. Specifically, a need for Amigen has been demonstrated in intractable diarrhea, ulcerative colitis and pancreatic fibrosis. In such conditions, proteins are often improperly hydrolyzed or poorly absorbed. Inability to metabolize protein properly may be important in the etiology of delayed fracture healing.

10. One liter of 5% Amigen - 5% Dextrose solution for parenteral administration may be prepared from one (50 Gm. can) of Amigen powder as follows:

a. All glassware and equipment used for preparation should be thoroughly cleansed, rendered pyrogen-free and sterilized before use.

b. Pour the contents of a 50 Gm. tin of Amigen powder onto the surface of 350 c.c. of warm (110 to 130° F.) pyrogen-free distilled water and dissolve with stirring.

c. Weigh 1/2 Gm. of solid sodium hydroxide, dissolve in 25 c.c. of distilled water and add to the above Amigen solution with stirring. Add an additional 100 c.c. of pyrogen-free water to make 500 c.c. of a 10% solution of Amigen.

NOTE: In the manufacture of Amigen powder the pH is controlled at 5.5, hence the addition of this amount of sodium hydroxide may be depended upon to increase the pH to 6.5, the level desired for parenteral use. The margin of safety of this neutralization procedure is very wide since, when unneutralized (pH 5.5), the solution causes no ill effects upon administration and when overneutralized (pH 7.5), a gross precipitation occurs upon autoclaving, indicating unsuitability for intravenous or subcutaneous injection.

d. Filter through lint-free, sterile filter paper into a liter bottle or flask. Filtration is speeded by the use of a fluted funnel, or by folding the filter paper or placing applicators between the paper and funnel.

e. Plug with lint-free material and immediately autoclave for not less than 15 minutes at 10 pounds pressure.

NOTE: Absorbent cotton enclosed in lint-retentive cloth makes a convenient plug.

f. The 10% solution thus prepared and sterilized by autoclaving is not stable and tends to deposit a fine sediment in from two to five weeks. This can be seen on the bottom of the container as a dust-like material which disappears in a small cloud when the bottle is whirled. Solutions with sediment should be discarded. The 10% solution may be stored at room temperature, although storage in a cold place will delay appearance of the sediment.

g. Mix equal volumes of the 10% Amigen solution and 10% Destrose solution aseptically in an infusion flask just before administration. This gives a final concentration of 5% Amigen and 5% Dextrose.

Precautions: Rigid asepsis is very important in the preparation and administration of Amigen solutions because such solutions are excellent media for bacterial growth. The following precautions must be carefully observed:

(1) A turbid solution indicates bacterial contamination and must be discarded.
(2) Discard if the solution contains any sediment or particulate matter.
(3) When a flask of Amigen solution has been opened, it should all be given during the injection. Any part not used must be discarded because of the danger of contamination.
(4) Amigen solutions should not be given from the same infusion apparatus as plasma without thorough cleansing, since the small amount of calcium in Amigen may react with the anticoagulant of the plasma if small amounts remain in the apparatus.
(5) Only clear, sterile, non-pyrogenic solutions should be injected.

Pyrogen: Amigen powder as manufactured is free from pyrogen, and adequate precautions must be taken that solutions made from the powder are also pyrogen-free. Water may contain pyrogen because (1) the receiver or glassware is contaminated, (2) the still is not properly designed with suitable baffles to prevent the entrainment of spray, (3) the water undergoing distillation is so heavily contaminated with pyrogen that a single distillation will not be adequate, (4) the still is run too close to maximum capacity, or (5) the distilled water is not promptly sterilized after collection.

11. To assure removal of pyrogens from glassware used in the preparation and administration of Amigen solutions, the glassware should be thoroughly washed with soap and water, rinsed with tap water and cleaning solution, again with tap water and finally with pyrogen-free distilled water. The glassware should then be allowed to dry, mouth down, and, within two hours of rinsing, be sterilized by autoclaving at 15 pounds pressure for 15 minutes.

Rubber tubing, through which plasma or crystalloids have been administered, may be rendered pyrogen-free for use with Amigen by immediately flushing out with large amounts of tap water and then with pyrogen-free distilled water, using one liter for each 30 to 40 inches of tubing. When used tubing cannot immediately be cared for in this manner, it should be put to soak in tap water until it can be cleansed and then boiled for 15 minutes in 5% sodium hydroxide, 5% sodium carbonate or 3% sodium phosphate. After boiling, the alkali should be removed by thorough flushing with tap water, rinsed with distilled water, dried and autoclaved at 15 pounds pressure for 15 minutes.

Needles may be prepared for use by cleaning with a solution of green soap and 5% phenol, rinsing with 70% alcohol and sterilizing with the tubing.

When reassembling a plasma set for use with Amigen, the filter may be omitted and the long delivery tube attached directly to the short needle connector.

12. The 5% Amigen - 5% Dextrose solution prepared as described and contained in a liter infusion flask stoppered with a standard rubber stopper is ready for immediate intravenous administration. The standard tubing and needles supplied with the plasma transfusion units or intravenous sets may be used in the same manner as they are used in giving plasma, glucose or saline. The 5% Amigen - 5% Dextrose solution prepared by the manufacturer for parenteral use is contained in a liter flask stoppered with a plain rubber stopper. Administration is most conveniently accomplished by the technic used to administer plasma.

13. No serious or anaphylactic reactions may be expected following the administration of properly prepared Amigen solutions. The appearance, during administration, of nausea and vomiting indicates too rapid intravenous injection. The speed of injection at which this reaction may occur varies in individuals. The average adult will tolerate the injection of a liter of Amigen 5% with Dextrose 5% over a period of two hours with no complaint.

14. Amigen solutions may safely be given subcutaneously and are usually absorbed rapidly. It is preferable that the solution be isotonic. Suitable solutions can readily be prepared by dilution of the 10% Amigen solution. The addition of two volumes of physiological saline to one volume of Amigen solution 10% gives the preferred solution for subcutaneous use.

15. A 5% or 10% solution of Amigen is suitable for oral or gastric tube feeding. Dilution with an equal volume of 10% or 20% Dextrose is preferable for jejunal or enterostomy tube feedings. It is best under all circumstances to feed small amounts frequently (50 to 150 c.c. per hour). The flavor of Amigen

may be improved by adding salt to a concentration of 0.5% NaCl or by dissolving in carbonated drinks or fruit juices.

16. The daily dosage of Amigen solution to be administered is the volume of solution required to cover the patient's protein needs. For practical purposes 1.0 Gm. of Amigen powder is equivalent to 1.0 Gm. of protein. The daily requirement for the normal adult is approximately 1.0 Gm. of protein per kilogram of body weight. For a protein-depleted patient 2.0 Gm. of protein per kilogram of body weight is the average daily requirement; 3.0 Gm. of protein per kilogram of body weight is the usual protein intake prescribed for children. This level may be required by adults suffering from severe protein depletion or severe burns; 5.0 Gm. of protein per kilogram of body weight is the daily requirement for the protein-depleted infant or child and occasionally for the protein-depleted adult who is rapidly losing protein.

When more than three liters of Amigen solution are required to meet the protein requirement, it is preferable to use oral or tube feeding in addition to parenteral administration.

17. The Bureau will appreciate receiving reports of Amigen-treated cases which are considered of unusual interest. In event of any untoward reactions following administration of Amigen, reports will be submitted giving the lot number and pertinent details.

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Chief of Bureau